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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,263	03/21/2002	Hermona Soreq	2391-00101	1307

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EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,263	SOREQ ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *6-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Detailed Action

Status of Application, Amendments, and/or Claims

Applicant's election with traverse of Invention I, (claims 1-5) in the Paper of 2 September 2003 is acknowledged. In addition, Applicant elected the following inventions: SEQ ID NO: 1 and "central nervous system stress". The Applicant traversed the restriction/lack-of-unity and argued that the antibody used in the present application should be rejoined with the method of using the antibody. However, Claims 1-5 (Invention I) and Claims 6-16 were restricted properly because the prior art discloses an antibody against a splice variant of the C-terminal of acetylcholinesterase (Boschetti, et al, 1996, Clinical Chem., 42(1): 19-23). This meets the limitations of the antibody recited in the first claimed invention. Therefore, none of the other claimed inventions can share a special technical feature with the first claimed invention. Despite Applicant's claims that the antibodies are different, Claim 1 of the instant Application does not recite an antibody based on a specific sequence (e.g., SEQ ID NO:) of a particular acetylcholinesterase, but rather on a variety of possible acetylcholinesterases. Therefore, the Boschetti, et al reference encompasses the claimed antibody of the instant Application.

Applicants also traversed the secondary restrictions. For example, the Applicant argued that the restriction based on the claimed conditions and diseases is improper because all the conditions and diseases can be diagnosed with the claimed antibody. However a search of each disease along with the antibody is an enormous and burdensome search. Similarly, a search of each disease or condition along with more than one elected SEQ ID NO is a burdensome search.

Claims 6-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as

being drawn to a non-elected Invention, there being no allowable generic or linking claim.

Claims 1-5 are under examination in the Instant Application.

Informalities

Specification

The disclosure is objected to because of the following informalities:

Abstract

The instant application is objected to because there is no Abstract of the Disclosure. See MPEP § 608.01(b). The Abstract should be submitted on a separate page and consist of a single paragraph of 150 words or less.

Appropriate correction is required.

Claim Rejections/Objections

Claim Objections

Claims 1 and 4 are objected to for reciting non-elected inventions (i.e., "blood-brain-barrier," "Alzheimer's disease," and SEQ ID NO: 2 and 3).

Claim Rejections - 35 USC § 112, first paragraph – scope of enablement.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 are rejected under 35 USC 112, first paragraph, because the specification, while being enabling for the antibody made against the acetylcholinesterase fragment peptide of SEQ ID NO: 1, to be used for identifying production of the AChE splice variant in the brains of mice, does not enable an antibody made against a variety of possible acetylcholinesterases for diagnosing central nervous system stress in animals or humans, or for identifying production of the AChE splice variant in animals other than mice. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with the claims.

The specification does not reasonably provide enablement for use of variants of acetylcholinesterase as recited in claims 1-5, except for the splice variant identified by the antibodies against SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The claims recite an antibody against a splice variant of acetylcholinesterase called *AChE-R*, identifiable by its atypical C-terminal. The claims embrace antibodies made against many or all variants of acetylcholinesterase identified by the presence of the I4 peptide.

The instant Application does not reasonably provide enablement for antibodies against a splice variant of AChE, except those identified by SEQ ID NO: 1, with the assurance that enabled antibodies that are functionally equivalent to those made against SEQ ID NO: 1 can be made without undue experimentation and with the assurance that they would have the desired properties of the claimed antibody against AChE-R. There are no examples of what specific

antibodies fall within the range of those that would bind an AChE splice variant.

The breadth of claims 1-5 is too large since the specification fails to provide any guidance on how to produce antibodies against AChE splice variants that still retain the function of the antibodies made against SEQ ID NO: 1. Claims 1-5 refer to any antibody that recognizes "one of the AChE-R splice variant[s] of acetylcholinesterase," without knowledge of the antibodies that would fall within this range. In other words, there is no discussion or working examples, in the instant case, as to what amino acid sequence in the antigen is necessary to produce an antibody with the functional characteristics of the claimed antibody. The instant claims suggest altering or deviating from antibodies made against the polypeptide disclosed in SEQ ID NO: 1, thus encompassing many variants of AChE.

Although enzyme family members often share several common structural features, antibodies made against an acetylcholinesterase will be very specific in terms of antigen selectivity. Therefore, it is not predictable as to which amino acids are necessary to maintain the characteristics of a protein antigen fragment in terms of the antibodies made against it. Furthermore, there is no evidence that the AChE-R splice variant is made in humans or other animals besides mice, except for its expression in certain cancers (Karpel, et al, 1994, Accession No. S71129).

Furthermore, Applicants have not demonstrated that they have diagnosed a "central nervous system stress," but instead demonstrated expression of the AChE-R variant in the hippocampi of mice forced to swim in the "confined swim stress" test. AChE-R splice variant expression is shown by Western blot in glioblastoma samples (Figure 1), labeled as "stressed" or

"non-stressed," as well as mice transfected with the glioblastoma AChE-R splice variant (Figure 2). Similar measurements were made in the cerebral spinal fluid of Alzheimer's disease patients, using an antibody against *alpha-ARP*, a protein with an unknown relationship or correlation to the AChE-R splice variant identified by SEQ ID NO: 1. Although the experiments with human CSF refer to "stressed" versus "non-stressed" humans, it should be kept in mind that stress is defined in a rather circular way in the instant Specification:

"Non-stressed humans" refers to patients in which no enhanced Omnipaque signal was detected by CT brain scan, while "stressed humans" refers to patients in which an enhanced Omnipaque signal was detected by CT brain scan" (Specification, page 20).

The specification does not enable use of the AChE-R antibody to diagnose a "central nervous system (CNS) stress." Since "central nervous system (CNS) stress" is poorly defined in the instant Specification, and may encompass a variety of neurological disorders (such as stroke, drug overdose and cancer, for example), and since the instant Specification is enabling only for identifying production of AChE-R in mice, a more specific phrase is needed to describe the condition the Applicant is intending to diagnose. The Specification describes use of antibodies made to SEQ ID NO: 1 to identify production of the AChE-R splice variant in mice hippocampi after the mice were subjected to a swim stress test. Aside from identification of the AChE-R splice variant in mice, diagnosis of a "central nervous system (CNS) stress", as claimed, is not adequately disclosed.

In summary, the specification does not provide a description of a repeatable process of producing, nor of working examples of making, all antibodies to acetylcholinesterase splice variants for the purpose of diagnosing "central nervous system stress." Nor can antibodies to

AChE-R be used to identify changes in the brain of humans or animals other than mice subjected to standard tests that provoke anxiety or fear. In addition, the predictability of the art is low with regards to the knowledge of what effects altering the sequence of the antigenic polypeptide would have on the antibody produced. For this reason, undue experimentation would be required to determine a structure-function relationship for each possible polypeptide encompassed by the claims.

Due to the large quantity of experimentation required to determine how to: use antibodies against splice variants of acetylcholinesterase to diagnose a "central nervous system (CNS) stress," the lack of direction or guidance in the specification regarding the conditions that can be diagnosed using such antibodies, the lack of working examples whereby "central nervous system (CNS) stress[es]" are identified or diagnosed, the state of the art showing the unpredictability of making antibodies against variant antigens, and the breadth of the claims which embrace innumerable antibodies against an acetylcholinesterase -undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

Claim Rejections- 35 USC § 102

The following are quotations of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being unpatentable over Boschetti, et al, 1996, Clinical Chem., 42(1): 19-23. Boschetti, et al disclose use of an antibody to distinguish between variant acetylcholinesterase. Additionally, the antibodies used by Boschetti, et al are made to the C-terminal of AChE and distinguish among several disorders, such as neural tube defects. This reference meets the limitations of claims 1-3 of "AChE-R splice variant" and "C-terminal peptide" and to be used to diagnose a central nervous system disorder that may be considered "stress."

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5 are rendered indefinite because of the phrase "central nervous system (CNS) stress," which is a conditional term that is poorly defined in the Specification (see the discussion of Enablement, above). "Stress" may refer to production of cortisol due to fear or anxiety, or may refer to trauma or a physiologically-demanding situation. The phrase "central nervous system" as related to stress encompasses a variety of diagnosable and non-diagnosable conditions, such as stroke and cancer.

This rejection can be overcome by supplying specific states or clinical conditions,

supported by the specification, which can be diagnosed using antibodies against SEQ ID NO: 1.

Conclusion: Claims 1-5 are rejected for the reasons recited above.

Claims 1 and 4 are objected to.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (703) 308-9346. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196

SLW

12/20/03

GARY KUNZ
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